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USE OF ANIMAL MODELS IN PERIODONTOLOGY A BRANCH OF DENTISTRY: A REVIEW OF ITS LITERATURE

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ABSTRACT

Non-human primates have been extensively used in periodontal research to investigate the pathogenesis of periodontal disease, Rats and hamsters are best suited for caries and calculus research. Ferrets may be a promising new model for studying periodontal disease and calculus formation. Beagle dogs are best suited for periodontal disease models than for caries or calculus formation. The purpose of this review is to evaluate animals as models for studying various aspects of human periodontal disease, including the disease process, its prevention and treatment.

KEYWORDS: Animal models, Experimental animals, periodontal diseases.

INTRODUCTION

To achieve on understanding of the life process, animals have been experimented on since long. This may be about the animals themselves, their physiology, their diseases and their treatment or behavior. Much of the knowledge is sought in the hope that it may be applicable to humans. In the field of periodontics, the first report appears to be that of Talbott (1899), who described periodontitis in mongrel dogs. For over hundred years, periodontal diseases have been studied in many species and a wealth of dependable data about periodontitis in species other than humans exists.

When these efforts are viewed in a historical context, it is extremely gratifying, to today's extra ordinary developments. The new information has been gained from 3 sources: Specific clinical observations including studies of site - specific microbiota, experiments on a variety of animal species and cell culture studies.[1]

Such experiments have provided cells and tissues of the pathologically altered host, and pharmacokinetics and treatment that are immediately relevant to treat humans with periodontitis.

Need for animal models

Animal research and its value to human experience remain controversial. Regardless of how much data can be presented, it is impossible to expect different species to respond identically or even similarly to the same challenge except within very narrow limits. Animal data can provide us with models of biologic trends before proceeding to human application.

Animal models have been used to evaluate the pathogenesis of periodontal diseases and various periodontal treatment modalities. Human longitudinal studies of periodontal diseases pose many problems such as determining the level of disease activity, individuals at risk and susceptibility to disease progression. It is important to choose an animal model that has similar characteristics of human anatomy and periodontal diseases. Features of periodontal diseases in human and animals vary greatly depending upon which form of the disease is present and the stage of the development.
In relatively new era of Periodontics like regenerative procedures, bone grafts and implant surgical procedures have shown promising results in animal studies. The

results obtained may serve to stimulate further efforts and promote further steps in the right direction.

Major Categories of Animal Models

Davidson et al (1987)[2]

There are 2 broad classes of models:

- Those based on analogy (Similar structures imply similar functions) and
- Those based as homology (Structures derived from the same evolutionary precursor have the same or similar function).

Four main categories of animal modes

1. Induced / experimental models, that attempt to reproduce conditions found in the original species
2. Spontaneous are natural models that are recognized as being similar to some conditions in the original species.
3. Negative or non-reactive models that are the normal counterparts of a disease model.
4. Orphan models that are animal diseases for which no human or animal counterpart is known.

Classification of animal models[2]

1. Small and inexpensive rodents such as mice, rats, hamsters, minks.
2. Larger animals like dogs, sheep
3. Non-human primates – Baboon, MaCaque, chimpanzee, gorilla
4. Various other species include ferrets, cats, horses, hedgehogs, pigs mangooses etc.

Mice

The healthy and diseased periodontium of the mouse has been studied in a large number of strains, most of which were highly inbred. (Deer mouse, RAP-albino, white Swiss- Webster, Swiss-albino, grey lethal and pocket mouse). Typical rodent dentition is I 1/1 C 0/0 PM 0/0 M 3/3. The periodontal tissues of the continuously growing incisors are rarely affected by periodontitis.

As soon as the molars attain functional occlusion and all throughout the life of the tooth, the crown is being worn down with relative rapidity because of the enamel-free areas of the cusps. To compensate for the occlusal wear, there is gradual deposition of cellular cementum at the apical end of each tooth, which keeps the teeth in occlusion.

Gilmore and Glickman stated that eruption of the molars of the mouse continues after initial contact is made with functional antagonists. The direction of eruption is bucco-occlusal. Accommodating this eruption, the buccal plate undergoes resorption along the periodontal surface and apposition along the periosteal surface, bone is deposited along the periodontal surface of the lingual plate, at the crests of the buccal and lingual plates and along the fundus of the alveolus. Cementum is deposited on the apical 3rd of root. Also, the junction epithelial shifts apically onto the root surface with age. Consequently, the distance between the crest of the alveolus and the CEJ increases, particularly at the lingual and palatal aspects of the mouse molars.[3]

There are disease resistant strains, but whether this results from genetic, dietary or bacterial factors is unknown at present. Whenever rampant disease has been observed, massive over growth of supra and sub-gingival bacteria, with tissue displacement and crater formation, has been the rule. For these reasons, periodontal disease in mice is greatly different from that observed in humans.

Rats

Rats have one set of teeth consisting of one incisor that is rootless and 3 molars in each quadrant. Physiological changes in the dentition occur throughout the life span of the rodent. There is rapid wear of the occlusal surfaces with continuous eruption of the teeth and apposition of cementum and bone. This causes progressive changes in tooth position, especially the molars that continuously move in an occlusal- distal- buccal direction. Most histologic features of the epithelium and connective tissue in the rat are similar to humans except for the sulcular epithelium, which is keratinized.[4]

One of the most successful approaches to studying oral disease in rats appears to be the utilization of the gnotobiotic or germ free rat. Gnotobiotic rats of the Sprague Dawley strain have been used to demonstrate the ability of various filamentous bacteria to form plaque and induce periodontal disease in the absence of other bacteria.[5]

Several gram-positive species of bacteria isolated from the human oral cavity were used as mono contaminants in rats, causing periodontal destruction in 84 days, (Actinomyces Viscosus, A.israelli)[4]

When gnotobiotic rats were monoinfected with a gram-negative anaerobic rod (A.a) or (Eik. corrodens), plaque adhering to the tooth surface was not formed. Once initiated, bone resorption occurred continuously rather than sporadically as in humans.[5]

In gram - free rats, however, there is considerable amount of impacted hair and bedding material between the teeth whose role in the disease process remains unclear. Lesions induced by gram-negative bacteria showed minimal inflammation. The connective tissue infiltrate contained primarily neutrophils, few lymphocytes, and no plasma cells. Thus, the destructive process in the response to gram-negative bacteria can occur in the absence of a cell-mediated immune response which is not similar to humans.[5]

Calculus formation can be studied in different strains of rats where diet seems to be the most consistent factor. Rats fed a sucrose rich diet developed a rapid proliferation and over growth of bacteria plaque, mainly gram positive, covering the molar fissures, the

interdental spaces and the marginal gingiva. This ultimately resulted in rounded or crater like gingival pockets. Therefore, it appears that the laboratory rat, although an acceptable model for studying calculus and caries has limitations as a model for periodontal disease. Periodontal disease in rats is different from that of humans. After inoculations of microorganisms into germ free rats, periodontal destruction occurs very rapidly, so there is no need for inducing disease with ligatures.[6]

The rat is relatively resistant to periodontal disease and is therefore mostly used for oral microflora research.

Another difference between the rat and human periodontal disease is that instead of the lesion extending along the root surfaces as in man, the most apical extend of the lesion is located along the central part of the inter dental tissues. Bone loss can occur without apical migration of the junctional epithelium.[7]

(Rat models -> Wistar Albino, Lewis, Norwegian grey, Kyoto and Carworth Wistar, Osborne - Mendel, Sprague – Dawley rats)

Hamsters

In the hamster, periodontal disease is a result of experimental and highly artificial conditions and in general, it does not seem to occur in animals living in a natural habitat. The strain most commonly used experimentally is the golden Syrian hamster, although the Chinese hamster and the cream – colored and the albino hamster have been studied as well.

The hamster dentition is of the rodent formula (I 1/1, M 3/3) and the molar begin to appear in the oral cavity between days 8 and 35 of postnatal life. The molars differs from that of rats and mice in that their crowns are completely covered by enamel. As in mice and rats, hamster molars erupt into the growing jaws and these are some evidence of their continuous eruption, occlusal wear, and shifting in the distal direction.[8]

There is an age related 'epithelial downgrowth' or an apical shift of the junctional epithelium which is more extensive on the lingual than on the buccal side of lower molars and corresponds with deposition of apical cementum.[9] The type of periodontal disease hamsters develop is similar to rats in that there is primarily gingival retraction with horizontal bone loss, the inter-dental septum being too narrow to induce intra-bony defects. Albino hamsters remain essentially disease free while the golden and cream-colored hamsters develop spontaneous periodontal disease when fed a high carbohydrate diet (King and Rowles 1955). They naturally harbor an infectious agent capable of inducing the disease when experimental conditions are favorable.

The disease can be induced in non-infected albinos by inoculating sub- gingival plaque from affected hamsters, and can be transmitted from generation to generation

Subepithelial inflammatory response characteristic of human gingivitis has not been identified for periodontal disease in the hamster. Hamsters have primarily been used for caries research due to the capability of the cariogenic microorganisms to form profuse amount of plaque and quickly develop carious lesions.[10]

Dogs

Dog is an excellent experimental animals to study gingival and periodontal diseases. Dogs are relatively small, easy to handle and extremely co-operative during experimentation. Their oral tissues especially the dento-gingival junction, the periodontium and the size of their teeth are quite similar to those of man, although there are gross anatomical, topographical and physiological differences.

The most frequently used and well-characterized species is the beagle, but mongrels, German pointers and others have been used as well. Dogs are used in dental research for the study of periodontal disease progression, Guided Tissue Regeneration; tissue wound healing and dental implants.

Differences exist between dog and man in the location of the inflammatory infiltrate in early gingivitis.

In the dog, the initial infiltrate located in the marginal part of the gingival, proceeds along the functional epithelium leaving the connective tissue in a relatively normal state. Gingivitis did not necessarily progress into periodontitis and a variety of factors may influence this conversion.[12]

Sheep

Sheep are largely domestic animals, but unlike dogs are bred in large numbers. There are many breeds of sheep, among them the Scottish Black face, Cheviot, Clun, Suffolk, Romney, Awassi, Loki and Kachhi, all of which have been studied with respect to their teeth.

Sheep are diphyodont; their deciduous dentition of 20 teeth has the formula I 0/3, C O/1, M 3/3 and their permanent dentition of 32 teeth has the formula I 0/3, C 0/1, PM 3/3, M 3/3.

In place of upper incisors and canines, sheep have a very broad, thick pad of tissue (the upper dental pad) against which the lower incisors and canines occlude. Lingual to the lower incisors, these is another but less broad but bulky shelf, the lower dental pad, which contacts the upper dental pad when the upper and lower jaws are brought into occlusion. Both the upper and lower dental pads consists of dense, collagenous connective tissues covered by keratinizing, stratified squamous epithelium with a thick and prominent stratum corneum. The lower dental pad actually represents an extension of the lingual gingival tissues, about 8 mm in width. Due to this tissue elevation next to the teeth, the lingual sulci are of 1.6 - 3.6 mm in probing depth.[13]

Non-Human Primates

In designing any medical or dental animal study, it is often advantageous to select an animal that is phycogenetically similar to humans. The wide range of non-human primate species allows appropriate selection for different investigations. Each species has unique similarities and dissimilarities to humans. Non-human primates have similar oral structures to humans and have naturally occurring dental plaque, calculus and gingivitis. The majority of non-human primates have similar deciduous permanent dental anatomy, although the sizes of teeth are dramatically smaller. The organization of collagen fibers in gingival and periodontal connective tissue is also similar to that of humans.

Clinically, healthy monkey gingiva is histologically indistinguishable from human gingiva. A shift in the composition of plaque flora from an early gingivitis to a later stage is also comparable to humans[14] Monkeys have been used widely as an animal model for studying periodontal surgical procedures. Smaller non-human primates such as marmosets have small oral cavities, which may preclude their use for certain periodontal procedures.

Ferrets

Use of the domestic ferrets as an animal modal in periodontics was originally described in the 1940s by King et al; who documented that the occurrence of periodontal disease in ferrets was similar to that occurring in humans (King 1954). The ferret has both a deciduous and permanent dentition. The permanent dentition consists of incisors, canine, 2^{nd}, 3^{rd} and 4^{th} premolar and 1^{st} and 2^{nd} molar.[15]

Harper et al and Mann et al have found ferrets to be a suitable model for the study of calculus. Calculus in ferrets has a physical structure similar to hydroxyapatite. The main difference is a lesser degree of calcification in the ferret deposits. Diet did influence the rate of formation, but not as much as in rats. Calculus in ferrets can be scored while the animal is alive, whereas this is not possible in rats. A study (Mann et al 1990) compared calculus formation in ferrets fed a mineral supplemented softened cat food and a twice-daily application of toothpaste containing pyrophosphate and a regular toothpaste. Results showed that the group treated with the pyrophosphate toothpaste produced significantly less calculus.[16]

CONCLUSION

There are remarkable variations in the features of periodontitis between one species to another. No genuine analogue of the various forms of human periodontitis exists in animals. Anatomic, physiologic, genetic, dietary and environmental factors, and habits are very important in the pathogenesis of the disease.

Analysis of the differences in the features of periodontitis between one species and another provides new insights into the nature of the disease. The features of periodontitis lesions in dogs resemble much more closely those seen in humans than the lesions in rodents and marmosets, although there are still marked differences.

In spite of the diversity of the manifestations of mammalian periodontitis, all species hold several common features.

1. Without exception, bacteria cause mammalian periodontitis.
2. Pocket formation is a universal manifestation of periodontitis in man and all other mammalian species in which the disease occurs.
3. Pocket formation is caused by the presence and invasion of bacteria.
4. Pathologic resorption of the alveolar bone is a feature of periodontitis in all-mammalian species.

It appears that a number of variables beyond control of the investigator are inherent in animal models currently available. Consequently, variability in results may be expected. However, there should also be room in the field of periodontal research for both clinical case reports and anecdotal reports on highly successful results in animals. We should not forget that, in reality, it is the singular best healing result, which demonstrates the ultimate potential of a given procedure.

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